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DECHERT
ATTN: ALLEN BLOOM, ESQ
4000 BELL ATLANTIC TOWER
1717 ARCH STREET
PHILADELPHIA, PA 19103

EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,456	BRUCK ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-63* is/are pending in the application.

4a) Of the above claim(s) *43-53 and 58-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-42 and 54-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/14/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Exhibit A (2 pages, seq. alignment).

DETAILED ACTION

Election/Restrictions

Applicant's election of group I, claims 35-42, and 54-57 in the reply filed on 04/07/2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 43-53, and 58-63 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 35-63 are pending. Claims 35-42, and 54-57 are examined on merits.

Specification

The disclosure at pages 35, 37, and 43 is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

Claim 42 is objected to because of the following informalities: the abbreviation for Celsius appears to be "C", not "C.". Note the attached definition of "Celsius" in Merriam-Webster dictionary downloaded from url>>>www.m-w.com on 6/26/2004. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 35, 36, 38-42, and 54-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 35, and 36 recite "an aligned contiguous segment of SEQ ID NO:2" but it is not clear what the metes and bounds are for. "Aligned" implies two sequence are brought together. For example, the two sequences are aligned at page 2 of Exhibit A. An "immunogenic fragment" of claim 35 or "the amino acid sequence" of claim 36 should be aligned with a contiguous segment of SEQ ID NO:2 in order to assess whether the sequence being compared to SEQ ID NO:2 is within the parameters set in the claims. However, the claims currently drafted appear to say that the claimed genus structure is compared with an alignment of SEQ ID NO:2 with some other sequence.

For the purpose of this Office action, the Office interprets "an aligned contiguous segment of SEQ ID NO:2" to be "a contiguous segment of SEQ ID NO:2". However, this treatment does not relieve applicant the burden of responding this rejection.

Claim 39 recites the limitation "the aligned sequence" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 40 recites the limitation "the aligned sequence" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 41 recites the limitation "the aligned sequence" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 42 recites the limitation "the filters" in line 7. There is insufficient antecedent basis for this limitation in the claim.

The dependent claims 38, and 54-57 are also rejected because the claims have the same unclear property boundary as the base claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35, 36, 38-42, and 54-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This written description rejection is made because claims 35, 36, 38-42, and 54-57 are interpreted as drawn to genus of proteins with various degree of variations from SEQ ID NO:2, wherein said genus when administered to a subject induces an immune response that recognizes a polypeptide having the sequence of SEQ ID NO:2.

The applicable standard for the written description requirement can be found: MPEP 2163; University of California v. Eli Lilly, 43 USPQ2d 1398 at 1407; PTO Written Description Guidelines; Enzo Biochem Inc. v. Gen-Prove Inc., 63 USPQ2d 1609; and Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

Claim 35, and the dependent claim 36 recite percent identity (i.e. 90 % or 95 %) to SEQ ID NO:2, but the claims do not recite a function coupled to the structure of the claimed genus. It is noted that the all of the claimed polypeptides should induce an immune response. However, "an immune response" does not appear to be the function coupled to the structure of the claimed genus because Ezzell (J. NIH Res, 1995, 7:46-49) teach at the paragraph bridging pages 47 and 48 that MAGE-1 and other structurally unrelated proteins to instant SEQ ID NO:2, induce the cell-mediated immune response. Likewise, Van den Eynde et al (J. Exp. Med. 1999, Vol. 190, pages 1793-1799) teach that the protein sequence shown at Figure 3, and many other proteins such as TRP1, or NY-ESO-1 that are all structurally unrelated to instant SEQ ID NO:2, also induce an immune response. Note Figure 2, and page 1798. The entity recognizing a polypeptide having the sequence of SEQ ID NO:2 in the instant claims 35, and 42 is not the

same entity as the claimed genus; in other words, activated T-cells or antibodies that are structurally different from the instantly claimed genus of polypeptides, recognize SEQ ID NO:2. Therefore, the limitation "wherein the isolated polypeptide, when administered to a subject in a suitable composition which can include an adjuvant or a suitable carrier coupled to the polypeptide, induces an immune response that recognizes a polypeptide having the sequence of SEQ ID NO:2" is not the function coupled to the structure of the claimed genus. Whether an antibody or a cytotoxic T cell (CTL) binds to a polypeptide would depend on the structure of said polypeptide. Thus, the limitation "wherein the isolated polypeptide, when administered to a subject in a suitable composition which can include an adjuvant or a suitable carrier coupled to the polypeptide, induces an immune response that recognizes a polypeptide having the sequence of SEQ ID NO:2" appears to be anther way of describing the structure of claimed polypeptides, not the function of the claimed polypeptide because antibodies or activated T cells bind to a polypeptide based on structure (epitope), not based on function of a polypeptide. Note Figure 3.1 (page 41) of Benjamini and Leskowitz (1991, Immunology, A Short Course, Wiley-Liss, Chapter 3, pages 37-45 only).

Claims 35 and 36 also lack written description because the claims as currently construed are drawn to genus of polypeptide **comprising** "an immunogenic **fragment**" or "the aligned contiguous **segment**" within its scope encompassing full-length proteins such as isoforms, allelic variants, and homologs that minimally contain said fragment or segment. There is substantial variability among the species of polypeptides. They are structurally unrelated.

Claim 42 as concurrently construed lacks written description, because the claimed genus of the polypeptides is encoded by a hybridizing strand (compliment or antisense strand) to a second strand that encodes SEQ ID NO:2. Unlike prokaryotic genome, the complimentary strand or antisense strand of a mammalian DNA encoding a protein does not encode a protein, except in a rare occasions. Instant SEQ ID NO:2 is encoded by a human gene. Although Van den Eynde et al., (cited above) teach one example of a human antisense strand encoding a protein, it appears to be a rare exception. Van den Eynde et al., are quite surprised by the discovery of a cryptic promoter started from an intron of another human gene. It is theoretically possible that the hybridizing nucleic acid molecules encode proteins, however, the instant specification does not teach the structure of a single species encoded by the hybridizing strands, thus, one of skill would not recognize the structure of the protein encoded by the first strand that hybridizes to the second strand, let alone a genus. The specification does not describe a single species encoded by the second hybridizing strand that could induce an immune response that recognizes a polypeptide having the sequence of SEQ ID NO:2, when the isolated polypeptide is administered to a subject

Claims 38, 39-41, and 54-57 depend on the rejected base claim 1, and the limitations in the dependent claims do not resolve lack of written description of the base claim, therefore rejected for the same reason stated for the base claim 35.

A description of a genus of proteins may be achieved by means of a recitation of a representative number, defined by amino acid sequences, falling

within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. Since the specification discloses only one species i.e. SEQ ID NO:2, and the breath of the claims includes proteins yet to be discovered, the lack of correlation between the structure and the function of the claimed genes, it is concluded that the written description requirement is not satisfied.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the genus of proteins, given that the specification has only described SEQ ID NO: 2. Therefore, SEQ ID NO:2, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

Claims 35-42, and 54-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making antibodies in a non-human subject, does not reasonably provide enablement for inducing immune response in a human subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to use and make the invention commensurate in scope with these claims. This rejection has multiple aspects.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

This scope of enablement rejection is made because the nature of the claimed invention is interpreted as drawn to SEQ ID NO:2 or similar variants for inducing an immune response in a human subject.

The specification discloses:

1) Overexpression of CASB168 mRNA (corresponding cDNA is SEQ ID NO:1 according to page 6-9) in colon samples from colon cancer patients as compared to normal control, is detected using real-time PCR (note at pages 34).
2) SEQ ID NO:1 is a full-length cDNA encoding a putative protein, SEQ ID NO:2 (note line 21 of page 37).
3) Putative HLA-A binding peptides derived from SEQ ID NO:2 at pages 43-45.

One cannot extrapolate the teaching of the specification to the claimed invention because the specification does not teach how to induce SEQ ID NO:2-specific immune response in a human subject using the claimed polypeptides. The specification provides no exemplification of or guidance on how to use the claimed genus to induce either B- or T-cell mediated immune response in a human subject. The specification does not disclose common structural attributes that stimulate an immune response in a subject that the claimed genus is from. There is insufficient guidance regarding the parameters and sequence of peptides that correlate with the ability to stimulate T cells and generate CTLs with claimed specifity/activity. There is insufficient guidance regarding selection of peptides that meet the instant criteria of stimulating an immune response. The specification at page 43-45 discloses putative HLA-A binding peptides derived from SEQ ID NO:2. However, the specification does not teach which(s) fragment of the numerous SEQ ID NO:2 fragments listed in the specification at pages 43-45 or other claimed peptides in the instant claims can be used to stimulate immune response in vivo human subject.

First, the specification does not even establish whether SEQ ID NO:2 is a cancer antigen, let alone how to induce either cell-mediated or antibody-mediated immune response against SEQ ID NO:2. The specification does not teach any biological or biochemical activity of SEQ ID NO:2. It is a newly discovered putative protein encoded by a human gene (note page 37 line 21). Although the instant application implies that SEQ ID NO:2 might be a human cancer antigen based on the mRNA expression data in colon cancer samples

(see the summary above), the specification does not disclose whether the protein overexpression is correlated with any in vivo tumor growth. The art recognizes that expression of mRNA does not dictate nor predict the translation of such mRNA into a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Thus, predictability of protein translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and

translation. For the above reasons, one of skill in the art would not be able to assume over-expression of SEQ ID NO:2 is associated with colon cancers.

Even if SEQ ID NO:2 is determined to be a colon cancer antigen, inducing an immune response against a cancer antigen that is also expressed in normal cells is not a trivial matter in the state of art. The relative skill in the art is low.

Riott et al., (Immunology, Fourth Edition, 1996, Mosby, pages 7.8-7.12, and Chapter 10 only) review that the immune system has two ways of responding to an antigen, in the instant case, SEQ ID NO:2, a putative colon cancer antigen based on the corresponding mRNA expression data. The first is the antibody-mediated response by which the immune system operates to destroy the antigen, and the second is the "cell-mediated" response, in which T cells recognizes cell-bound antigen in association with MHC molecules. MHC class I and class II act as guidance systems for T cells. This is known as MHC restriction. Only a minority of peptide fragments from a protein antigen is able to bind particular MHC molecules. Different MHC molecules bind different sets of peptides. Riott et al., teach at Fig. 7.22 and Fig. 7.23, and also page 7.10, right column that the peptides sizes 12-15 are optimal for MHC molecule class I and certain amino acids at certain positions are critical for binding to MHC class I.

US Pat. 5,840,839 (Nov. 24, 1998) teaches at column 19 that finding peptides that bind a MHC molecule and stimulate an immune response, is not a trivial matter. The '839 patent at column 19, lines 53 to 67 teaches that structure of a T cell epitope that stimulates an immune response in context of MHC molecules is unpredictable in the current state of art. The '839 patent at columns

19-20, and Table 1 teaches that the various candidate T cell epitopes selected based on theoretical binding motif of one class of MHC molecule, i.e. HLA-A31 do not work when they are experimentally tested as shown in Table 1. This suggests that theoretically selected T cell binding motifs as disclosed at pages 43-45 of the instant specification have to be tested experimentally in order to determine whether they are actually T cell epitopes or not.

The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. Ezzell (J. NIH Res, 1995, 7:46-49) teaches that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, para 6). In addition, Spitler (Cancer Biotherapy, 1995, 10: 1-3) recognizes the lack of predictability of the nature of the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: cancer vaccines don't work. Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1). Furthermore, Boon (Adv Can Res, 1992, 58:177-210) teaches even if activated CTLs are significantly increased, the therapeutic success remains unpredictable

due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph).

As for B-cell mediated immune response part of enablement rejection, Benjamini and Leskowitz (cited above) at page 38, first sentence under the heading "Foreignness" teach "Animals normally do not respond immunologically to self." Thus, it is highly unlikely that instant SEQ ID NO:2 or similar proteins would induce any B-cell mediated immune response against SEQ ID NO:2 or similar proteins in a human subject.

The specification provides insufficient guidance with regard to theses issues and provides no working examples of a peptide that would work with any MHC molecule in inducing an immune response in a human subject. Considering the state of art, the broad scope of claims in respect to the nature of peptide and also to the nature of MHC molecules, it is concluded that that undue experimentation is required to practice the full scope of the claimed invention. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to make the alleged discovery, not how to screen it for themselves.

Claim Rejections - 35 USC § 101

Claims 35-42, and 54-57 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well established utility.

This utility rejection is made because the claims 35-42, and 54-57 are interpreted as drawn to the newly discovered polypeptide, SEQ ID NO:2 and

similar variants. The asserted utility in inducing cell-mediated immune response is not substantial because the specification does not even establish whether SEQ ID NO:2 is a cancer antigen, let alone how to induce either cell-mediated or antibody-mediated immune response against SEQ ID NO:2. The specification does not teach wither SEQ ID NO:2 is overexpressed or underexpressed in any human disease. The specification does not teach any biological or biochemical activity of SEQ ID NO:2. SEQ ID NO:2 is a putative protein (without any known function) encoded by a newly discovered human cDNA i.e. SEQ ID NO:1. Although the instant application implies that SEQ ID NO:2 might be a human cancer antigen based on the mRNA expression data in colon cancer (see the specification summary above), the specification does not disclose whether the protein overexpression is correlated with any in vivo tumor growth. The art recognizes that expression of mRNA does not dictate nor predict the translation of such mRNA into a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which

mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Thus, predictability of protein translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. For the above reasons, one of skill in the art would not be able to predict over-expression of SEQ ID NO:1 could be used as biomarker for colon cancer.

The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a substantial utility. The proposed use of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed nucleic acids. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696.

Claims 35-42, and 54-57 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth

above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 35, 36, 38-41, and 54 rejected under 35 U.S.C. 102(b) as being anticipated by Mankovich et al., (1989, Journal of Bacteriology, vol. 171, pages 5325-31) as evidenced by Benjamini and Leskowitz (1991, Immunology, A Short Course, Wiley-Liss, Chapter 3, pages 37-45 only).

Claims 35, 36, 38-41, and 54 are interpreted as drawn to an isolated polypeptide or fusion protein (claim 38) comprising an immunogenic peptide fragment (claim 35) or segment (36) of SEQ ID NO:2, or composition (claim 54) comprising said fragment. The claims do not define the size of the peptide fragment or segment that is "an immunogenic fragment". However, the specification at page 3, line 4 contemplates an epitope of at least 7 contiguous amino acids of SEQ ID NO:2 is within the scope of the claims.

Mankovich et al., at page 5328 (note Fig. 2) teach an isolated polypeptide comprising a fragment 100 % identical to amino acid 98 to 105 of instant SEQ ID NO:2 Note Exhibit A (two pages, a sequence alignment). Mankovich et al., teach a composition comprising the polypeptide and other ingredients for loading

said polypeptide in SDS-PAGE gel shown at Fig. 4, and also teach that the polypeptide is fused with LacZ at its N-terminus. Note the abstract, and Fig. 3.

Benjamini and Leskowitz (1991, cited above) is cited to present evidence that the fusion polypeptide of the prior art when administered to a subject would induce an immune response that recognizes a polypeptide having the sequence of SEQ ID NO:2.

Benjamini and Leskowitz at page 41 teach that all proteins are immunogenic in an appropriate subject. Proteins in general are multi-determinant antigens, with several distinct epitopes (note Figure 3.1). Benjamini and Leskowitz at page 43, 1st paragraph teach "An immunologic reaction in which the immune components, either cells or antibodies, react with two molecules that share epitopes, but are otherwise dissimilar, is called a cross-reaction. When two compounds cross-react immunologically, it means that the compounds have one or more epitopes in common and that the immune response to one of the compounds recognizes one or more of the same epitope(s) on the other compound and reacts with it." Benjamini and Leskowitz at page 44 teach "There are other examples of immunological cross-reactivity, wherein the two cross-reacting substances are unrelated to each other except that they have one or more epitopes in common. These substances are referred to as heterophile antigens. For example, human blood group A antigen reacts with antiserum raised against pneumococcal capsular polysaccharide (type XIV). Similarly, human blood group B antigen reacts with antibodies to certain strains of Escherichia coli. In these examples of cross-reactivity, the antigens of the

microorganisms are referred as the heterophile antigens (with respect to the blood group antigen)."

In the absence of evidence to the contrary, it is the Office's position that the immunogen of Mankovich et al., i.e. the mutL from Salmonella typhimurium shown at Fig. 2 (page 5328) when administered to an appropriate subject, is able to induce an immune response that recognizes the epitope of amino acid 98 to 105 of instant SEQ ID NO:2. In other words, the mutL would act as a heterophile antigen with respect to the instant SEQ ID NO:2 since the two proteins have one epitope in common that would result in cross-reactivity.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 55-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mankovich et al., (1989, Journal of Bacteriology, vol. 171, pages 5325-31) in view of WO 95/17210 (29 June 1995)

This rejection is made because claims 55-57 are interpreted as drawn to an immunogenic composition comprising a polypeptide comprising an immunogenic fragment that share a common epitope with the instant SEQ ID NO:2, and an adjuvant, more specifically 3D-MPL (a TH1-type inducer according to the specification at page 18, lines 1-5).

As stated in the 102 (b) rejection above, the primary reference, Mankovich et al., teach a polypeptide comprising an immunogenic fragment that share a common epitope with the instant SEQ ID NO:2. Note the 102 (b) rejection above for a further detail.

Mankovich et al., do not teach composition comprising an TH1-type inducing adjuvant.

However, the WO 95/17210 at pages 11 and 12, Figure 2a, for example teaches that the TH1-type inducing 3D-MPL and other adjuvants also stimulate a higher production of antibodies.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to add adjuvants to enhance a higher production of the antibodies to the immunogen of the primary reference in animals. One of ordinary skill would have been motivated to combine the immunogen and the instantly claimed adjuvant(s) to get higher yield of the antibodies from a given animal, thereby reducing unnecessary sacrifice of animals and at the same time reducing cost associated with buying animals for the production of antibodies.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina C Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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MISOOK YU, Ph.D.
Examiner
Art Unit 1642